Discontinuation of antiepileptic drugs in seizure-free patients – when and how?

In seizure-free patients with epilepsy, the question of whether, and if so when, it is acceptable to discontinue treatment may be difficult to answer. A thorough risk-benefit assessment should be undertaken with the patient and next of kin, during which the consequences of a relapse must be weighed against the disadvantages of continued use of the drug. As a general rule, adult patients should have been seizure-free for at least two years before discontinuation is considered. In children with epilepsy where the prognosis is known to be good, discontinuation may be considered earlier.

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MAIN MESSAGE

Adult patients with epilepsy should have been seizure-free for at least two years before withdrawal of antiepileptic drugs is considered

In children who have a type of epilepsy with good prognosis, discontinuation of antiepileptic drugs *may* be considered earlier

Risks and benefits of discontinuation must be discussed carefully with the patient and next of kin

If seizures recur after withdrawal, the vast majority of patients regain control of their seizures by resuming the same drug treatment as previously

With the use of antiepileptic drugs, 60–70 % of patients with newly diagnosed epilepsy become seizure-free (1). Although drug treatment could gradually be discontinued in many of these patients, it is not unusual for it to continue. Some patients and their next of kin raise questions about the justification for this. The assessment as to *whether* antiepileptic drugs should be withdrawn, and if so *when*, is a difficult issue for both clinician and patient.

The purpose of this article is to provide a brief overview of the arguments for and against discontinuing antiepileptic treatment. It is based on current studies identified through a literature search using the search terms «antiepileptic drug withdrawal/discontinuation, adults, children», followed by a discretionary literature review, in addition to the authors' own experience. We also provide some practical advice on this decision-making process.

Arguments *in support of* withdrawal

More than half of those who use antiepileptic drugs report adverse effects (2), and many are concerned about these effects in the long-term (3). Many parents are particularly worried about the impact that the use of these drugs may have on the child's development and learning (4, 5). It has been shown that use of antiepileptic drugs may have a negative effect on cognitive function in both children and adults (4, 6) and that cognitive performance improves after withdrawal (7, 8).

Antiepileptic drugs may also affect behaviour, mood and alertness (2), as well as having a negative effect on the lipid profile as well as endocrine and cardiac function. A Norwegian study showed that discontinuation caused a reversal of these adverse effects (9–11).

Many types of childhood epilepsies show the widest variation in prognosis. Permanent remission is almost always seen in around 15 % of these, and in children who have a type of epilepsy with good prognosis, discontinuation should always be attempted (12). Because 50–60 % of all children with epilepsy may achieve freedom from seizures without drugs 10–20 years after onset of seizures (12), the question of discontinuation should be discussed for *all* children who have become seizure-free. Account must nevertheless be taken of the factors in Box 1 (7, 13–15).

By withdrawing the use of drugs, it is possible not only to prevent chronic adverse effects, but also to avoid interactions with other drugs and possible teratogenic effects during pregnancy. Moreover, many patients find themselves «certified as healthy» when they no longer need to take drugs every day. Unnecessary use of drugs also represents a cost to society.

Seizure recurrence after withdrawal indicates the need for continued medication.

Arguments *against* withdrawal

A little less than 70 % of patients achieve good control of seizures with antiepileptic drugs (1), and these minimise the effect of epilepsy on their lives. A number of the new drugs appear to have a better adverse effect profile than the older enzyme inducers (2, 3), providing security and protection against seizure-related accidents.

Seizure recurrence constitutes not only a mental strain, but may also have other serious consequences (13) – for example, the loss of the patient's driving licence, with all that this entails. Some risk losing their job if this requires a driving licence or if seizures may endanger the life and health of the patient and/or others. Psychosocial problems are an additional factor, including stigmatisation and, in the worst case, sudden unex-

BOX 1

Clinical factors that increase the risk of seizure recurrence after discontinuation of antiepileptic drugs in children (7, 13–15)

Early onset of seizures (< 2 years)

Onset of seizures in adolescence (> 10 years)

Symptomatic epilepsy (seizure-generating substrate determined on MRI scan)

Special epilepsy syndromes, e.g. Lennox-Gastaut syndrome or juvenile myoclonic epilepsy

Neurological deficit

Several types of seizure

Developmental delay

Use of more than one antiepileptic drug

Pathological EEG, epileptiform activity or slow background activity

pected death in epilepsy, SUDEP, although this is fortunately rare (16–18).

The withdrawal of seizure-preventing drugs causes seizure recurrence in 15–41 % of patients (7, 13). However, it is important to remember that 7–20 % of seizure-free patients who continue with drugs will also experience seizure recurrence within a period of 1–2 years (7, 13).

Few robust studies

There are few robust studies in this field (19). With regard to adults, two studies exist in which seizure-free patients were randomised either to discontinuation or continued treatment.

A prospective, open randomised study of 1 013 patients who had been seizure-free for at least two years found recurrence in 41 % two years after discontinuation, compared to 22 % in the group that continued to receive treatment (13).

The second study, a Norwegian randomised, double-blind study, included 160 patients who had been seizure-free on monotherapy for at least two years. They were randomised to discontinuation (n = 79) or continued treatment (n = 81). After 12 months, 15 % of those in the discontinuation group and 7 % in the group receiving continued treatment experienced seizure recurrence. In an open follow-up study, 89 % of patients who were randomly selected for continued treatment chose to discontinue the drug. After 41 months, seizures had recurred in 27 % of those who had discontinued treatment (7).

The explanation for the relatively low percentage of recurrence in this study compared to that of the first study may be that the inclusion criteria in the later study were more stringent. Both studies found that the risk of seizures in those patients who discontinued antiepileptic drugs was twice as high as in those who continued.

A meta-analysis based on 25 observational studies reported seizure recurrence in 25 % after one year and in 29 % two years after discontinuation (20). An American guideline based on 17 observational studies concluded with a similar rate after discontinuation of 31.2 % for children and 39.4 % for adults (21).

Regarding children, an overview is available based on 12 observational studies of more than 2 500 children. This showed seizure recurrence in 4–33 % of the children one year after discontinuation and in 9–39 % after two years. The variation in recurrence rate is probably attributable to differences in the type of epilepsy, its aetiology, and additional disorders in the children included in the study. The risk of seizure recurrence was highest in the first 12 months (22).

A Cochrane review based on five studies of altogether more than 900 children concluded that there was a 34 % increased risk of seizure recurrence if the child had been seizure-free for less than two years, compared with those who discontinued drug use after more than two years of freedom from seizures. The risk of recurrence with early discontinuation was further increased if the child had focal seizures, developmental delay and/or a pathological EEG result (23).

In the case of pharmacoresistant epilepsy, that is, in patients with intractable seizures after trying two relevant antiepileptic drugs, other forms of treatment should be considered. Of those who are found to be suitable for resective epilepsy surgery following a thorough assessment, around 60 % are seizure-free after temporal lobe resection, while 30–40 % are seizure-free after extratemporal surgery (24). The majority of those who are seizure-free two years after the surgery continue to be so in subsequent years. However, some experience seizure recurrence after many seizure-free years, even with continued use of antiepileptic drugs (24, 25).

No randomised controlled studies have been conducted on patients who discontinue antiepileptic drugs after epilepsy surgery. Several of the observational studies in this field show selection bias – usually those with the best prospects for continued freedom from seizures are selected for discontinuation (25).

Predictors for seizure recurrence

For some patients the risk of recurrence after discontinuation is greater than for others. However, it has been difficult to find consistent predictors of seizure recurrence (26). Boxes 1–3 show the presumed main risk factors in adults and children respectively, and in those who have undergone epilepsy surgery. It is important to emphasise that none of these factors alone constitutes a contraindication for withdrawal, but a combination of several such factors increases the risk (26). Neurological deficit in patients before discontinuation has been shown to be an independent negative predictor (7, 13). Our experience indicates that caution should be exercised with regard to discontinuing drugs in patients with a structural brain lesion, pathological EEG and focal seizures with impaired awareness.

In some forms of childhood epilepsy, for example benign neonatal and infantile seizures, benign rolandic epilepsy and Panayiotopoulos syndrome, almost all patients achieve remission. If drug treatment has been initiated in these patients, its total duration should always be planned. When considering discontinuation, it is essential to take account of factors that increase and factors that reduce the risk of recurrence – age at onset of epilepsy, cause of epilepsy, type of epilepsy, EEG findings and additional neurological and developmental disorders, cf. Boxes 1–4 (14, 22, 27).

Following surgery, epileptiform activity on EEG and residual changes on MRI increase the risk of seizure recurrence on discontinuation, cf. Box 3.

Seizure control after resumption of treatment?

The vast majority of patients will become seizure-free when they resume taking the drugs that originally controlled their seizures. Although the results of studies in this field differ, there are indications of a more than 80 % chance of patients regaining control of

BOX 2

Clinical factors that increase the risk of seizure recurrence after discontinuation of antiepileptic drugs in adults (14, 15)

Late onset of seizures (> 16 år)

Generalised epileptiform EEG disturbances in the last year

Information regarding myoclonic seizures, focal seizures with impaired awareness and/or tonic-clonic seizures

Seizure after start of treatment

Use of more than one antiepileptic drug

Neurological outcomes

BOX 3

Clinical factors that increase the risk of seizure recurrence after discontinuation of antiepileptic drugs in patients following epilepsy surgery (14, 15)

Older than 30 years at time of surgery

Epilepsy of long duration

Early discontinuation (< 2 years after the procedure)

Persistent focal seizures with preserved awareness

Relapse after previous attempt at discontinuation

Postoperative epileptiform EEG disturbances

Indications of cerebral gliosis or residual changes on postoperative MRI

Focal cortical dysplasia as epilepsy aetiology

Neurological outcomes

seizures if they reinstate the same drug at the same dosage as previously (28, 29).

Discussion and some practical advice

No definite knowledge exists as to the optimal time to cease treatment for seizure-free patients (30). As a general rule, we believe that both children and adults should have been seizure-free for a minimum of two years. In cases of childhood epilepsy that based on experience frequently goes into remission, it is possible to consider discontinuation earlier. Also in those who become seizure-free after epilepsy surgery, we would recommend waiting to discontinue drug treatment until two years after the procedure. In some cases, a simplification of treatment may be relevant somewhat earlier – from polytherapy to monotherapy – particularly if the patient experiences unpleasant adverse effects.

In children who still have carers around them and in those who have not yet started work or do not have a driving licence, the risk of injury caused by possible seizures must be weighed against the risk of the effect on the child's development and learning if drug treatment is continued. This, and the fact that the chance of final remission is somewhat higher in children than in adults, is part of the reason that the threshold for attempting withdrawal of treatment is lower in children than in adults.

If there is recurrence after discontinuation, this does not unequivocally imply lifelong treatment. There may be good reasons to try again at a later point in time, even though the threshold for attempted discontinuation is slightly higher in such cases.

The risk of recurrence is not significantly different depending on whether the drugs are tapered off rapidly (six weeks) or slowly (nine months) (30). Based on our clinical experience, if the choice is made to discontinue antiepileptic drugs, we would recommend withdrawal over a period of at least eight weeks. For withdrawal of phenobarbital or clonazepam we recommend 12–24 weeks.

No certain knowledge exists as to whether stopping treatment affects the long-term prognosis in patients who have either become seizure-free with antiepileptic drugs or following epilepsy surgery. It is a matter of debate whether discontinuation in the first group merely reveals the natural course of the epilepsy, and in the other unmasks the true postoperative outcome (14).

The decision to discontinue treatment with antiepileptic drugs is a specialist responsibility. The question should be discussed carefully with the patient and if relevant the next of kin, weighing up the benefit and risk. Since no two patients have precisely the same risk profile, the decision must be made individually based on the patient's risk factors for seizure recurrence. It is important to discuss the many possible consequences of a relapse and listen carefully to the preferences of the patient and any next of kin. If the choice is made to continue the treatment, the risk of long-term adverse effects ought to be considered, as well as the possibility to prevent these (3).

BOX 4

Factors that suggest successful discontinuation of antiepileptic drugs (14)

Freedom from seizures for more than two years

Rapid freedom from seizures after start of treatment

Normal neurological status and normal psychomotor development

Normal EEG and normal brain MRI

Type of epilepsy with known good prognosis

Onset of seizures in childhood (2–10 years)

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